REMARKS

The Office Action dated March 25, 2004, has been received and reviewed. Claims 9-11, 16-18 and 22 were rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, the Office Action alleges the specification does not enable the therapeutic use of antisense mediated inhibition, based in general upon the contention that the clinical application of antisense therapy is highly unpredictable. Applicants respectfully traverse this rejection.

Applicants note that the "test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." (MPEP §2164.01, citing *In re Wands*, 858 F.2d 731, 737). Furthermore, the test for whether or not the enablement requirement has been met involves determining whether or not practice of the invention as claimed involves "undue experimentation". It has long been settled that "the key word is 'undue', not 'experimentation'". *In re Angstadt*, 190 USPQ 214, 219 (C.C.P.A. 1976).

For the presently claimed application, Applicants submit that the application of the current technology requires routine effort, and not undue experimentation. Applicants submit that antisense nucleotides have been shown to treat cancer. Furthermore, Applicants submit that Claims 9-11, 16-18 and 22 list a group of sequences and fragments that can readily be assembled by one of skill in the art to make and or use the present invention. Applicants include with this response an article by Umberto Galderisi et al. that discloses the use of oligonucleotides as selective inhibitors of gene expression as well as the first antisense-based drug. *Journal of Cellular Physiology*, 181:251-257 (1999). It was found that the antisense oligonucleotide Fomivirsen, was very useful for the treatment of cytomegalovirus (CMV) retinitis in patients with AIDS. Phase III trials have been completed on this drug and it has been approved for the market. Therefore, antisense technology has been successfully employed in the treatment of a

disease state. Applicants have also included a copy of the abstract relating to the Fomivirsen study.

Applicants have also include a paper by Burkhart et al., illustrating the use of antisense oligonucleotides to investigate, both *in vitro* and *in vivo*, the therapeutic potential of inhibiting hMYCN expression. *J. National Cancer Institute,* 95:18 1394-1403 (2004). Applicants have additionally included an article by Geary et al. that illustrates the development of potent, pharmacologically active, specific antisense oligonucleotides. *Drug Metabolism and Disposition*, 31:11 1419-1428 (2003). Applicants also include an article by Smith et al. that illustrates that antisense oligonecleotides inhibits pancreatic cancer growth. *Cancer Letters*, 135:1 107-112(6) (1998). Additionally, Applicants include an article by Rudin et al. illustrating antisense oligonucleotide taken up by cells illustrating antitumor activity in early phase clinical trials. *Journal of Clinical Oncology,* 22:6 1110-1117 (2004). Applicants would be happy to produce more articles illustrating the successful use of antisense technology to further demonstrate that one of skill in the art could readily use the oligonucleotides recited to treat a subject afflicted with cancer as recited in Claims 9-11, 16-18 and 22.

Applicants note that the description of the present application includes the report of the inhibition of E-selectin-mediated adenocarcinoma cell adhesion by stable transfection of antisense sequences directed at the human Lewis (1,3/1,4) fucosyltransferase gene, FUT3. Specifically, the metastatic parental cell line, HT-29LMM, expressed high levels of sialyl Lewis x, sialyl Lewis a, (1,3/1,4)fucosyltransferase activity, and FUT3 transcript, but antisense transfectant cell lines did not. The stable antisense clones were unable to colonize the liver when they were injected into the spleens of nude mice. These results provide target validation for inhibition of carcinoma metastasis with antisense FUT sequences and confirm the primacy of (1,3)fucosyltransferases in the synthesis of selectin ligands. *See,* page 14, lines 16-29. Furthermore, figure 8, which depicts flow cytometry of surface antigens on COLO-205 and stable antisense transfectants, confirmed that the synthesis of sialyl Lewis x and sialyl Lewis a is inhibited in the antisense clones. Additionally, table 5 shows the

results of *in vivo* growth assays that indicate that expression of antisense FUT sequences is capable of inhibiting colon carcinoma growth *in vivo*.

The specification also discloses that the present example shows the disruption of sialyl Lewis x/a biosynthesis and inhibition of colon carcinoma cell proliferation by stable transfection of antisense sequences directed at the human Lewis (1,3/1,4)fucosyltransferase gene, FUT3, and the plasma (1,3)fucosyltransferase gene, FUT6. The subcutaneous tumors created by injection of nude mice with antisense transfectant cell lines grew more slowly than those arising from control COLO-205 and sense transfectants which illustrates that these results provide target validation for inhibition of colon carcinoma proliferation with antisense sequences directed at human FUT genes. *See*, page 25, lines 1-14. Therefore, Claims 9-11, 16-18 and 22 are enabled.

Applicants additionally note that disclosure in the specification of an actual reduction to practice is *not* necessary to satisfy the enablement requirement (*see*, MPEP §2164.02; *Gould v. Quigg*, 822 F.2d 1074, 1078; 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987)). Accordingly, Applicants submit that there is sufficient guidance to direct a person of skill in the art to use the nucleotides as claimed. Applicants submit that one of skill in the art could readily formulate the oligonucleotides claimed. Moreover, the Court of Appeals for the Federal Circuit has held that it is not necessary for the specification or claims to list all operative embodiments, or to exclude all inoperative embodiments, stating: "Even if some of the claimed combinations [are] inoperative, the claims are not necessarily invalid. 'It is not a function of the claims to specifically exclude ... possible inoperative substances...'". *Atlas Powder Co. v. DuPont* , 750 F.2d 1569; 224 USPQ 409 (CAFC 1984). All that is required by § 112 is that one skilled in the art may determine the inoperative embodiments with no more than routine skill. Applicants submit that this standard is satisfied in the present application. And that one of skill in the art would readily be able to follow the invention as presently claimed. Accordingly, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. § rejections to Claims 9-11, 16-18 and 22.

CONCLUSION

In view of the remarks presented herein, Applicants respectfully submit that the claims define patentable subject matter. If, in the opinion of the Examiner, a telephonic conference would expedite the examination of this matter, the Examiner is invited to call the undersigned attorney at (919) 854-1400.

It is not believed that an extension of time and/or additional fee(s)-including fees for net addition of claims-are required, beyond those that may otherwise be provided for in documents accompanying this paper. In the event, however, that an extension of time is necessary to allow consideration of this paper, such an extension is hereby petitioned under 37 C.F.R. §1.136(a). Any additional fees believed to be due in connection with this paper may be charged to our Deposit Account No. 50-0220.

Respectfully Submitted,

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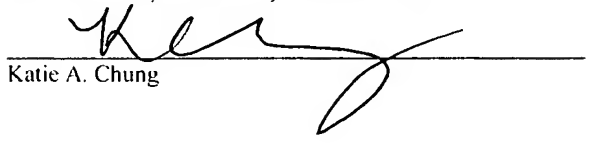

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